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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,772	03/30/2001	Beat Mollet	88265-4011	6428

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Allan A. Fanucci
WINSTON & STRAWN
200 Park Avenue
New York, NY 10166

EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,772	MOLLET ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *9-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 March 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *N?A* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-14 are still at issue and are present for examination.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-8, in Paper No. 8, is acknowledged. The traversal is on the ground(s) that a review of any prior art references that disclose the specific bacterial strains would require that any references that disclose the use of the strains to be examined as well, thus as the claim groupings are sufficiently related, the search and examination of the method of use claims (Group II) in addition to the product claims (Group I) should not impose an additional burden on the examiner. This argument is not found persuasive fro the following: As was previously stated, inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the *B. subtilis* strains can be used in methods of screening for genes involved in the production of isovaleric acids. Further while a search of each of the groups would overlap, they are not coextensive. For example, a search of Group II would require search of subclass 435/267 and 435/277 , a search of which would be unnecessary the search of the elected group I.

Finally, applicant is reminded that the instant "method of use" claims differ in the scope of the "product" used such that the searches that must be conducted prior to the determination of patentability are also different.

The requirement is still deemed proper and is therefore made FINAL.

Claims 9-14 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 8.

Priority

Applicants statements that this application is a continuation of the U.S. national stage designation of International Application PCT/EP99/06818 filed September 15, 1999, the content of which is expressly incorporated herein by reference thereto is acknowledged. It is noted that this application is a continuation of International Application PCT/EP99/06818 filed September 15, 1999, not the national stage designation of this application as stated above.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate

paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Applicants filing of information disclosures, filed 3/3/2001, is acknowledged. Those references considered have been initialed. EPO 0643922 has not been considered because applicants have not supplied a translation of this document.

Drawings

The drawings filed on 3/30/2001 are objected to for the reasons stated on the enclosed form PTO-948. Note, applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Specification

The disclosure is objected to because of the following informalities:

As stated above under the priority section, this application is a continuation of International Application PCT/EP99/06818 filed September 15, 1999, not the national stage designation of this application as stated above.

Appropriate correction is required.

Claim Objections

Claims 1 is objected to because of the following informalities:

Claim 1recite "isovaleric acids" and "iso-valeric acids". It is suggested that applicants maintain consistency throughout the application.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (2-8 dependent on) is indefinite in that it is unclear in the recitation "A bacterial strain of the B. subtilis group..." It is unclear what is encompassed in the "B. subtilis group", beyond that of the species *B. subtilis*. Following this rejection, claims 2-8 each are drawn to the B. subtilis strain of claim 1 or a claim dependent from claim 1. If it is applicants intent that bacterial strains other than B. subtilis species are encompassed by "B. subtilis group", then claims 2-8 would lack proper antecedent basis and be rejected as such. It is suggested that applicants amend claim 1 such as "A bacterial strain of *B. subtilis*..." to overcome this rejection.

Claim 1 is further indefinite in that the recitation "...genes involved in the biosynthesis of isovaleric acids..." is unclear. It is unclear what the metes and bounds of the group of genes considered to be "genes involved in the biosynthesis of isovaleric acids..." are.

Claim 1 is further indefinite in that the recitation "...substantial amounts of iso-valeric acids..." is unclear. What is a substantial amount of isovaleric acid?

Claim 2 is indefinite in that the recitation "...taste perceptible amounts of iso-valeric acids" is unclear. As taste is specific to the person that is tasting, and different individuals are able to taste differently, this limitation in the claim is indefinite.

Claim 4 is indefinite in that the recitation "...wherein the modified gene(s) is derived from the *ywfL* gene" is unclear. What is encompassed by the *ywfL* gene and what is encompassed by those modified genes that are derived from the *ywfL* gene? Absent a specific nucleic acid sequence it is unclear what is considered to be the *ywfL* gene.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-6 and 8 are directed to all possible bacterial strains of the *B. subtilis* group, wherein one or more genes involved in the biosynthesis of isovaleric acids have been modified such that the strain cannot produce substantial amounts of isovaleric acid. The specification, however, only provides a single representative species, B. natto I-20767, encompassed by these claims. The specification also fails to describe additional representative species of these bacterial strains by any identifying structural

characteristics or properties other than the strain cannot produce substantial amounts of iso-valeric acid, as recited in claim 1, for which no predictability of structure is apparent. Further, applicants have not described any additional genes involved in the biosynthesis of isovaleric acids or any modifications of said genes beyond the ywfL gene and its deletion. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-6 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *B. subtilis* strain, wherein the *ywfL* gene has been deleted, such that the strain cannot produce substantial amounts of isovaleric acid, does not reasonably provide enablement for any bacterial strain of the *B. subtilis* group, wherein one or more genes involved in the biosynthesis of isovaleric acids have been modified such that the strain cannot produce substantial amounts of isovaleric acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-6 and 8 are so broad as to encompass any bacterial strain of the *B. subtilis* group, wherein one or more genes involved in the biosynthesis of isovaleric acids have been modified such that the strain cannot produce substantial amounts of isovaleric acid. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of bacterial strains broadly encompassed by the claims, including all bacterial strains of the *B. subtilis* group, wherein one or more genes involved in the biosynthesis of isovaleric acids have been modified. Since the proteins expressed by the bacterial strain determine the structural and enzymatic makeup of the bacterial strain, predictability of how changes in the strain's protein expression profile affects the desired enzymatic reactions requires a knowledge of and guidance with regard to how each of these proteins and the resulting enzymatic products effects other proteins and other enzymatic reactions. Further, the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of

and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a *B. subtilis* strain, wherein the *ywfL* gene has been deleted, such that the strain cannot produce substantial amounts of isovaleric acid.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any bacterial strain with any modification that results in a decrease in the amount of isovaleric acid produced because the specification does not establish: (A) those proteins and regions thereof the protein structure which may be modified to result in the desired activity; (B) the general tolerance of the bacterial strain to such modifications and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleic acid residue of a gene involved in the biosynthesis of isovaleric acid, with an expectation of obtaining the desired biological function; and (D) the

specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to effect the bacterial strain such that the strain cannot produce a substantial amount of isovaleric acid and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those bacterial strains of the claimed genus having the claimed reduction in the production of isovaleric acid.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any bacterial strain of the *B. subtilis* group. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those bacterial strains having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention of claim 7 is appears to be drawn to a novel *B. subtilis* strain I-2077. Since the *B. subtilis* strain I-2077 is the invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The organism is not fully disclosed, nor has it been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the *B. subtilis* strain I-2077 in accordance with 37 CFR 1.801-1.809.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sekiguchi et al. (JP 55004382, 1/30/1980).

Sekiguchi et al. teach a method of fermenting soybeans with *Bacillus natto* in the presence of gluconic acid or gluconolactone to produce natto. The gluconate improves natto flavor and aroma by inhibiting formation of isovaleric acid.

One of ordinary skill in the art would be motivated to produce a Bacillus natto strain with a random mutation, such that one or more genes involved in the biosynthesis of isovaleric acid is modified such that the strain cannot produce a substantial amount of isovaleric acid. The reasonable expectation of success comes from the high degree of skill and knowledge in the art in the area of random mutation and screening for mutants with desirable properties, such as a reduced ability to produce isovaleric acid.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
December 11, 2002